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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
GRASER, JENNIFER E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,084	LALVANI ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,23,24,26-28 and 95* is/are pending in the application.

4a) Of the above claim(s) *23,24,26-28 and 95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-19 (SEQ ID NO:1), in the reply filed on 1/23/08 is acknowledged. The traversal is on the ground(s) that examination of all of the Groups would not place a serious burden on the Examiner. They argue that at the very least, Group IV (claims 27-28) should be kept with elected Group I. This is not found persuasive because the kit of claims 27 and 28 allow for analogues which are not included in the method recited in claim 1 and they also comprise a medication (product to treat or prevent) which is not required in the method of Group I and, therefore, the kit is not for the exact process claimed. Accordingly, it would place a serious burden on the Examiner to perform a separate literature search as the search between the Groups would not be coextensive. Applicants have argued that there should be a species election and not a Restriction Requirement of the peptides recited in claim 16. If claim 1 were limited to ESAT-6 as the antigen (since an ESAT-6 epitope was elected; SEQ ID NO: 1), then the peptides in claim 16 which are from this antigen would be searched in a Species manner as suggested by Applicant. It is noted that no International Search Report was prepared for claims 22-25, 27-28, 50-51, 71-73 and 92-94 which correspond to the instantly pending claims as they are unduly broad. The EPO determined that the claims relate to such an extremely large number of possible products which may be obtained from any pathogen that a meaningful search over the whole of the claimed scope was not possible. The claims still contain such an unduly broad scope that even a proper Restriction was difficult to

establish. Claim 1 is drawn to such a large range of polypeptides and antigens from completely different sources that it was difficult to assess the invention. The requirement is still deemed proper and is therefore made **FINAL**.

Claims 23, 24, 26-28 and 95 are withdrawn from consideration as being drawn to a non-elected invention.

Specification

2. The disclosure is objected to because of the following informalities

It is noted that pages 7-8 and 21-22 of the instant specification recites amino acid/nucleic sequences which are encompassed by the definitions for nucleotide sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). The M.P.E.P., Section 2422.02, 37 CFR 1.821(b) requires exclusive conformance, with regard to the manner in which the nucleotide/amino acid sequences are presented and described, with the sequence rules for all applications that include nucleotide sequences that fall within the definitions. It appears that these sequence are included in the CRF. Accordingly, the specification should be updated to include the appropriate sequence identification number immediately following each sequence.

If this is not the case:

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is unclear what is encompassed by an agent any 'pathogen, vaccine or any other *moiety* which induces a cellular response". The metes and bounds of this description cannot be understood. The agent is essential to the claimed method. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. This broad description of an agent by generic name, e.g., pathogen, moiety or vaccine', is not sufficient to allow for one to understand the invention. It is unclear what structures are actually used in the claimed method. Clarification and correction is required.

Claim 1 is also vague and indefinite because it recites a protein 'having a length of at least 30 amino acids' versus a peptide. This is vague and confusing because it appears a protein of 30 amino acids is a peptide and not a full-length protein which appears to be the requirement in the specification for a functional assay. Additionally, if the protein can be small as 30 amino acids in length, what are the size limitations on the peptide? Clarification and correction is requested.

Claim 1 is also vague and indefinite because it does not require the agent to be a protein, nor does it require the peptide epitope to be from the protein recited in the claim

which seems to be a requirement for the method to work. The claim as written allows for the peptide to be from any protein contained in any moiety, pathogen or vaccine. Clarification and correction is required.

Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there is no reaction step. It is unclear how one determines degree of recognition. What is considered a 'greater extent'? There are not active steps. How is it determined whether the T cells recognize the protein? There is no contact step. Most importantly, the specification appears to indicate that in order to accurately diagnose recent exposure more than one time point is needed to determine and identify those that were asymptomatic at time of testing and slower to mount immune response. The claims should include the appropriate time points, e.,g as indicated on page 17.

Claim 1 is vague and indefinite because it is unclear what is considered a 'greater extent'. The term "greater extent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 2 is vague and indefinite because it is unclear what is encompassed by the phrase 'a greater reaction'. What type of reaction is this? Clarification and correction is requested.

Claims 3-11 are vague and indefinite because it is unclear what is encompassed by an 'analogue of the protein". What structures represent these analogues? How is

the analog related to the protein? Is it a functional or structural analog, etc.? Clarification and correction is required.

Claim 5 contains no correlation step and therefore incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Steps (i) and (ii) recite determining reaction of the T cells to the peptides or analogs but do not tell you what this means, nor is it clear why two different populations are taken. Are these populations taken at the same time point or different time points? Additionally, claim 5 should be amended to recite 'further comprising" in the preamble if this is indeed what is intended as these steps appear to be in addition to those of claim 1.

Claim 6 is vague and indefinite because the term "substantially (no reaction)" is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 7 is vague and confusing because it only requires the protein to comprise 'at least the amino acid sequence of the peptide epitope". If the protein is only the peptide epitope, then it is no different from the peptide epitope and the assay would not be able to detect the difference in binding from the protein (a single epitope as defined in the claim) or the epitope since they would be identical. Clarification and correction is required.

Claims 7, 8, 9, 10 and 11 recite the limitation "analogoue". There is insufficient antecedent basis for this limitation in these claims as claim 1 does not recite the term 'analogue' or include analogs.

Claim 9 is vague and confusing because it is unclear whether the epitopes are all contained within the protein. Additionally, are these epitopes being recognized at a 'greater extent' or merely being recognized? This dependent claim is confusing as how it applies to claim 1.

Claim 10 is vague and confusing because if all of the possible epitopes from the protein were being used, it does not appear there would be any difference in recognition detected. The method in the specification appears to rely on the difference between different stages of infection having the ability to recognized shorter peptides versus the full-length protein containing all of the epitopes. Accordingly, this claim appears to result in a non-functional detection method. Clarification and/or correction is requested.

Claim 11 is vague and confusing because it is unclear how one would insure that antigen presenting cells were present.

Claims 12-16 appear to contain non-elected subject matter since the elected peptide epitope is from the ESAT-6 protein of Mycobacterium it would not have the ability to detect the other virus, bacterial and intracellular pathogens recited therein. Accordingly, the claims should be amended accordingly. As stated in the response to the Restriction Requirement above, if claim 1 were limited to use of ESAT-6 then a species election would apply to all of the sequences in claim 16 which are peptide epitopes from ESAT-6.

Claim Rejections - 35 USC § 112-Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification teaches a tuberculosis diagnostic test which can detect the difference from those recently exposed versus those with long-term infection. It was known in the prior art that following exposure to *M.tuberculosis* individuals have an approximately 10% risk of progressing to active tuberculosis with disease symptoms within one to two years. If the active tuberculosis does not manifest within the first 1-2 years then the residual risk of progress to active tuberculosis is 5% over the remaining lifetime of the individual. (specification page 1). *M.tuberculosis* diagnostic tests were known in the prior art to have unique problems as due to the use of BCG (closely related to M.tuberculosis) as a vaccine against tuberculosis individuals who have been vaccinated with BCG can react positively to the tuberculin skin test. Additionally, culturing of mycobacterium can take up to 8 weeks so identification tests are not always practical and obtaining the samples is often done through invasive procedures. See Lalvani et al. WO00/26248. The invention seeks to overcome the problems of the prior

art and have the ability to detect those recently exposed from those with long-term infection. However, the instant claims are very broadly drawn to a diagnostic assay for exposure to ***any*** agent through the use of any pathogen, vaccine, moiety, etc.. This includes a wide array of different viruses, parasites, bacteria, etc.. The specification provides no working examples of any of these other assays, nor does it provide a single example of a particular protein and peptide epitope from the agent, with the exception of the ESAT-6 and CFP10 proteins of *M.tuberculosis*, which would have the ability to detect exposure to any other pathogen. All of the listed pathogens encompassed in claim 1 and further recited in claims 12 and 13 have completely different modes of infection and disease symptoms, as well as different virulence factors and different proteins. They do not have the unique problem of chronic infection and/or conversion to active infection at a much later date as is encountered with *M.tuberculosis* infection. The instant method appears to be unique to *M.tuberculosis* infection. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the

invention." This requirement has not been met with regards to detection of recent exposure to any other agent than *M.tuberculosis*. The claims should be limited to diagnosing in an individual recent exposure to *M.tuberculosis* as it would take undue experimentation on the part of one skilled in the art to develop diagnostic methods for detection of any other pathogen, which would include identifying relative proteins and peptide epitopes which would have the ability to function as is taught in the instant specification. This is akin to discovery and not mere routine experimentation. Working examples are only directed to the use of ELISPOT for the detection of *M.tuberculosis* exposure. The specification has found that T cells from individuals recently exposed to *M.tuberculosis* react to whole proteins from the pathogen but do not react to, or show substantially less reaction, to peptide epitopes from the pathogens. It is believed T cells appear in the later course of infection and are more mature and focused and would not be present in individual recently exposed to M.tuberculosis (specification, page 2). Additionally, the method requires knowledge or a protein and specific epitopes which are unique to the agent being tested. For instance, given the similiarity of BCG to M.tuberculosis those exposed to BCG often test positive for tuberculosis exposure. However, BCG does not have the ESAT-6 gene and therefore can distinguish between patients with tuberculosis and patients who have been vaccinated with BCG. See WO 00/26248 paragraph bridging pages 1-2. This is vastly important. It would take undue experimentation for one of ordinary skill in the art to identify agents which could be detected in the claimed assay as it would involve discovery of appropriate, unique polypeptides and identification of their optimal epitopes. Additionally, it is unclear that

agents from other pathogens, moieties or viruses would have the ability in this assay to determine recent exposure from long-term infection as the disease patterns and progressions of other pathogens vary so greatly from *M.tuberculosis*. Many pathogens do not have the problem of chronic, latent infection or seroconversion.

The specification has is also only enabled for diagnosing recent exposure to *M.tuberculosis* in a host wherein the peptide epitopes are one of SEQ ID NOs: 1-17 and the protein is ESAT-6 (or non-elected protein CFP-10 and SEQ ID Nos: 18-35). The instant claims recite the use of a protein 'having a length of at least 30 amino acids'. This is vague and confusing because it appears a protein of 30 amino acids is a peptide and not a full-length protein which appears to be the requirement in the specification for a functional assay. The specification does not enable this scope as it has only shown results versus recognition of the full-length protein of ESAT-6 versus its peptide epitopes for use in distinguishing latent infection from recent exposure. The claims should be limited accordingly. Additionally, the instant claims should include the method steps from the ELISPOT assay as it is unclear and no description is provided for other means of detection. The specification teaches that using ex vivo ELISPOT assay T cells from the individuals exposed M.tuberculosis reacted to antigen from the pathogen at 3 months from exposure, but no longer reacted to antigen at 6 months from the exposure thereby indicating the individuals had cleared the infection which was detected initially. Therefore, it was determined that testing at a subsequent time point would avoid the treatment of individuals who naturally clear infection. Individuals that did not react at 3 months, but did react at 6 months from exposure were mounting a

slower weaker response to infection and more likely to progress to active disease. This group is desirable for treatment. The instant specification teaches that the inventors have shown that effector T cells specific for mycobacterial antigen increase markedly prior to the onset of active symptomatic mycobacterial infection thus detection of this increase in effector T cells is a good predictor of progression or susceptibility to progression to disease in asymptomatic latently infected individuals.

The specification is also not enabled for the use of any protein, any peptide epitopes and especially any analogs of these proteins/peptides. The specification is only enabled for diagnosing recent exposure to *M.tuberculosis* in a host wherein the peptide epitopes are one of SEQ ID NOs: 1-17 and the protein is ESAT-6 (or non-elected protein CFP-10 and SEQ ID Nos: 18-35). The breadth of the instant claims are drawn to a method using polypeptides which are not specified in the sequence disclosure or even mentioned in descriptive terms, e.g., name, molecular weight, etc.. "Analogs" as encompassed in the instant claims include substitutions, additions, or deletions to be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein or peptide to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding,

catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native protein. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. The prior art further teaches that amino acids

owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Most importantly, the specification fails to identify what is encompassed by the term 'analog' (of the protein or peptide epitope).

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

7. ***Closest prior art, not relied on:***

a) Lalvani et al (WO 00/26248).

Lalvani et al disclose a method of diagnosing in host infection by exposure to a mycobacterium which expresses ESAT-6 comprising contacting a population of T cells from the host with one or more peptides or analogs. The peptide recited in SEQ ID NO: 1 is specifically disclosed. Lalvani et al do acknowledge on page 24, lines 2-10, that in tuberculosis-endemic countries, where a significant proportion of healthy individuals are latently infected with M.tuberculosis, the specificity of an assay based on the detection of a M.tuberculosis-sensitized cellular immune system might be lower than in their study. They also acknowledge that the assay has not been validated in children, where tuberculosis is usually a primary infection and presents acutely. In Example 6 the method does compare the use of whole ESAT-6 for detection of T cell responses versus peptides from ESAT-6. They found that peptides are able to elicit a response from both CD4 and CD8 T cells and more patients could be detected using peptides than the

whole protein. See page 25 Example 6. This is the opposite of what is being detected in the instantly claimed methods, e.g., detecting the *protein* to a greater extent than the peptides to diagnose recent exposure. Lalvani et al do not teach diagnosing in an individual 'recent exposure to the agent', nor does it teach or suggest whether the individual can recognize a protein of at least 30 amino acids (ESAT-6) to a greater extent than one or more peptide agents as is required by the instant claims.

b) Andersen et al (US Patent No. 5,955,077).

Andersen et al teach that ongoing or previous M.tuberculosis infection may be detected by using ESAT-6 polypeptides (see column 14, lines 35-65); however they do not teach or suggest a method which involves determining whether an individual has been recently exposed to the pathogen by having the ability to recognize ESAT-6 protein to a greater extent than a peptide epitope from ESAT-6.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Shanon Foley, can be reached on (571) 272-0898.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645